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(54) **Controlled release pharmaceutical preparation.**

(57) A controlled release pharmaceutical preperation comprising a core containing e medicinal compound and a coating layer containing a water-repellent salt and a weter-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl group. Said preparation releases a medicinal compound in a sigmoid type dissolution pattern irrespective of the PH of a dissolution medium.

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The present invention relates to a controlled release pharmaceutical preparation, and more particularly to a so-called sigmoid type controlled release pharmaceutical preparation (Sigmoidal-Releasing System) from which a medicinal compound rapidly dissolves after a certain lag time.

Hitherto, concerning pharmaceutical preparations containing medicinal compounds, there have been various attempts to maintain their effects after the administration. For example, following two pharmaceutical preparations have been known. One is a sustained release pharmaceutical preparation (see Japanese Unexamined Patent Publication No. 156617/1985) in which a core is alterately coated with two compositions, namely, with a coating composition comprising a water-soluble polymer such as a polyvinyl alcohol or polyvinylpyrrolidone and a water-insoluble polymer such as ethylcellulose, polyvinyl chloride or Eudragit RS (trade mark, from Röhm Pharma, Germany), and a composition comprising diltiazem hydrochloride, an organic acid and a lubricant to form multi coating layers. And the other is a sustained release pharmaceutical preparation (see Japanese Unexamined Patent Publication No. 193913/1985) in which a core containing a medicinal active ingredient and an organic acid is spray-coated with an ethanol solution of an acrylic polymer having trimethylammoniumethyl group.

However, although these pharmaceutical preparations are suitable for releasing medicinal active ingredients gradually after the administration, they have a problem that the starting of the dissolution of their medicinal active ingredients can hardly be controlled.

On the other hand, it is known in the field of the pharmaceutical preparation that an increase in the thickness of the coating layer results a delay of the starting of the dissolution of a medicinal active ingredient. However, it is also known that in this case the thick coat layer hinders rapid dissolution of a medicinal active ingredient after the starting of the dissolution and therefore an effective blood concentration can not be obtained rapidly.

An object of this invention is to provide a controlled release pharmaceutical preparation giving a so-called sigmoid type dissolution pattern wherein a lag time until the starting of the dissolution of a medicinal compound and the rate of the following dissolution can be controlled and the rate of the dissolution of the medicinal compound does not depend on the pH of a medium for the dissolution.

This and other objects of the present invention will be come apparent from the description hereinafter.

It has been found that in case of coating a medicinal active ingredient with a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl group and a water-repellent salt such as magnesium stearate or calcium stearate, ① the time until the starting of the dissolution of a medicinal active ingredient from the pharmaceutical preparation lengthens, ② the time until the starting of the dissolution can be controlled by the amount of the coating layer and ③ once the dissolution starts, almost 100 % of the medicinal active ingredient dissolves irrespective of the amount of the coating layer.

The present invention provides a controlled release pharmaceutical preparation comprising a core containing a medicinal compound and a coating layer containing a water-repellent salt and a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl group.

Fig. 1 is a graph showing the result of the dissolution test with water as to various controlled release granules (a) to (e) obtained in Test Example 1 which differ from each other in the amount of coating layer. Fig. 2 is a graph showing the result of the dissolution test with water, first fluid and second fluid as to the controlled release granule (d) obtained in Test Example 1. Fig. 3 is a graph showing the change in blood concentration of a medicinal compound in case that the granule (d) was administered to dogs in Test Example 2. Fig. 4 is a graph showing the result of the dissolution test as to a capsule containing various controlled release granules obtained in Test Example 3 which differ from each other in the amount of the coating layer.

The controlled release pharmaceutical preparation of the present invention comprises a core containing a medicinal compound and a coating layer containing a water-repellent salt and a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl group, which surrounds said core. If desired, another coating layer of at least one material selected from the group consisting of ethylcellulose, hydroxypropylcellulose and a medicinal compound may be provided around said coating layer in the controlled release pharmaceutical preparation of the present invention.

In the present invention, a polymer of acrylic acid, methyl acrylate, ethyl acrylate, methacrylic acid, methyl methacrylate, ethyl methacrylate or the like, which has trimethylammoniumethyl group in the molecule, may be used as a water-insoluble and slightly water-permeable acrylic polymer constituting the coating layer. For instance, a copolymer of ethyl acrylate, methyl methacrylate and β-acryloyloxyethyltrimethylammonium chloride in which about 0.025 to about 0.033 mole of β-acryloyloxyethyltrimethylammonium chloride is contained per mole of the other neutral acrylic monomers is preferably used. Such copolymer is, for example, commercially available under trade mark "Eudragit RS" from Röhm Pharma, Germany or the like.

The above-mentioned polymer may contain, for instance, a small quantity of a water-permeable polymer. Such copolymer is, for example, commercially available under trade mark "Eudragit RL" from Röhm Pharma, Germany or the like.

As ethylcellulose or hydroxypropylcellulose which is a material of another coating layer provided around th coeting leyer of en ecrylic polymer, for instance, ethylcellulose containing about 46.5 to about 51.0 % of thoxy group, hydroxypropylcellulose containing about 53.4 to about 77.5 % of hydroxypropoxy group or the like can be suitably used.

As a weter-repellent salt which constitute the coating layer with an acrylic polymer, a salt of higher fatty acid and an alkaline earth metal is preferably used. Concretely, examples of the salts are calcium stearate, megneclum steerete and the like.

In the present invention, as the ratio of the above-mentioned acrylic polymer and the water-repellent salt in the coating layer, it is adequate that about 0.5 to about 5 parts by weight, preferably about 1.5 to about 4.5 perts by welght and more preferebly ebout 2 to ebout 4 perts by welght of the ecrylic polymer is contained per part by weight of the water-repellent salt.

The amount of the coating layer for the core is verlable a little depending on the form or the size of the core. However, it is preferable that the amount of the coating layer to be used tends to increase a bit depending on the increase of the surface area per unit weight, that is, the decrease of the particle size of the core. For example, in case of spherical perticles heving mean perticle size of ebout 500 to ebout 1000 μm, the emount of the coating layer is about 5 to about 80 %, preferably about 7 to about 50 %, in particular, preferably about 8 to about 30 %, based on the weight of the core.

In the present invention, the form of the core to be coated is not particularly limited and various forms such as plain tablet, pill, granule and fine granule may be suitably used. Above all, the granulated cores having mean perticle size of ebout 300 to ebout 5000 μm, in perticuler, ebout 500 to about 1500 μm may be preferably used.

The medicinal compound to be contained in the core is not particularly limited. For instance, calcium antagonists such as diltiazem hydrochloride, verapamil hydrochloride, nicardipine, nitrendipine and nimodipine, antiesthmetic egents such es theophylline end trimetaquinol, water soluble vitemins, entiblotics, entimelignatumor agents, antipyretic analgesics, antihyperglycemic agents and the like may be used.

In addition, various additives such es an excipient, a binder, a lubricant, an eggregation-preventing agent and a solubilizer for a medicinal compound which are usually used in this field may be contained in the core.

Examples of excipients are sugars such as sucrose, lactose, mannitol and glucose, starch, crystalline cellulose, calcium phosphete, calcium sulfate, celcium lectate end the like. Examples of carriers for reguleting particle sizes are sucrose, lactose, starch, crystalline cellulose and the like. Examples of binders are polyvinylalcohol, polyacrylic acid, polymethacrylic acid, polyvinylpyrrolidone, glucose, sucrose, lactose, maltose, sorbitol, mannitol, hydroxyethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, macrogols, arabic gum, gelatin, agar, starch end the like. Examples of lubricants are stearic acid, talc and the like. Examples of aggregetion-preventing agents ere the ebove-mentioned lubricants, sillcone dioxide, colloidel sillcone dioxide and the like. Examples of solubilizers for medicinal compounds are organic acids such as fumaric acid, succinic acid and malic acid and the like.

* Excipients

The pharmeceutical preperation of the present invention can be prepared by coeting cores conteining e medicinal compound with a dispersion of a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl group and e water-repellent salt. The preparation of the cores can be carried out according to the usual procedure for the preparation, for example, as described in Lemingtons Pharmaceutical Sciences 17, 1603-1632, 1633-1643 (Mack Publishing Company, published in 1985). For Example, the cores can be prepered by granuleting the composition of e medicinal compound, e binder and, as occasion demends, other additives such as an exicipent according to the method of wet oscillating granulation, rotating granulation, fluidizing bed granulation or the like to obtain granules. Alternatively, for example, the cores may be prepared using carriers for regulating particle sizes. That is, spherically granulated carriers may be coated with a medicinal compound according to the usual method such as powder coating method to obtain the cores. Powder coeting can be carried out, for instance, by greduelly edding e medicinel compound or a mixture of the medicinel compound and suitable additives such as an excipient with spraying a solution obtained by dissolving a binder in e suitable solvent such as water, a lower elcohol such as methanol, ethanol, propenol, isopropanol or butanol, a lower elkanone such es ecetone or methylethylketone, chloroform, dichloromethene, dichloroethene or e mixture thereof, on carrier particles to be cores, according to the method of rotating granulation, pan coating, fluidizing bed coating or the like.

The coeting for thus obtained cores can be carried out by edhering a dispersion of e water-repellent salt and an acrylic polymer to the cores followed by drying.

As a dispersion medium for the ebove-mentioned component of the coeting layer, water, en alcohol such es methanol, ethanol or propanol, e ketone such as acetone, e halogenated hydrocarbon such as methylenechlorid or chloroform, e mixture thereof or the like is exemplified. Weter, an alcohol or a mixture thereof is preferable, and ethanol or a mixture of ethanol and water is particularly preferable.

The coating can be carried out according to e method generelly used in the art for preparation such as the

method of fluidizing bed coating or pan coating. For example, in case of th method of fluidizing bed coating, th coating can be carried out es follows. Thet Is, while the cores ar fluidlzed In en epparatus by meens of elr pressure, they are spray-coated with an aqueous dispersion of a water-repellent salt and an acrylic acid polymer at an adequate rate from the nozzl of the spray-gun.

The concentration of a water-repellent salt and an acrylic polymer In the dispersion is not perticularly limited, but it is preferable that these components are added within the above-mentioned scope of the preferable proportion of both components, to be the concentration of ebout 5 to about 40 % by weight. In eddition, e plasticizer, a coloring agent and the like may be contained in the dispersion. As a plasticizer, for instance, triacetin, triethyl citrate, acetyltributyl citrate, diethyl phthalate, polyethyleneglycol, polysorbate or the like can be suitably used. The emount of the plesticizer to be used Is preferebly ebout 5 to ebout 40 % by welght based on the welght of en acrylic polymer.

The drying of thus obtained coating leyer can be easlly carried out, for example, by heating at about 35 to about 100°C, particularly about 40 to about 70°C.

The other form of the pharmaceutical preparation of the present invention wherein another coating layer made of et leest one materiel selected from the group consisting of ethylcellulose, hydroxypropylcellulose end a medicinal compound is provided around the coating layer containing a water-repellent salt and a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl group, can be easily prepared by further coating the above-mentioned pharmaceutical preparation having the coating layer of an acrylic polymer with these components according to the usual method.

For exemple, In case of coeting with ethylcellulose or hydroxypropylcellulose, the solution prepered by dissolving ethylcellulose or hydroxypropylcellulose in water, methanol, ethanol, acetone or a mixed solvent thereof to be the concentration of about 0.5 to about 10 %, may be sprayed for coating. In case of coating with a medicinel compound, the solution or dispersion contalning seld medicinel compound or e mixture of the medicinel compound and suitable additives such as an excipient and e binder may be sprayed for coating according to the usual method. As the edditives, for Instance, the above-mentioned binders and excipients may be suitably used.

Thus obtained controlled release pharmaceutical preparation of the present invention may be administered as It is or In a form filled In capsules.

The pharmaceutical preparation of the present invention has the following characteristics because of its coating leyer of a slightly water-permeable acrylic polymer. That is, a medicinal active ingredient rapidly dissolves from the preparation after a certain period which depends upon the amount of the coating layer although it never dissolves after administration until the certain time passes. Besides, the time until the start of the dissolution of e medicinel ective Ingredient Is optionelly adjustable by chenging the amount of the coeting leyer.

Therefore, the pharmaceutical preparation of the present invention is useful as a pharmaceutical preparation wherein the starting of the dissolution of a pharmaceutical compound can be adjusted by itself. And it is further useful thet the pharmeceutical preperation which can retein en effective blood concentration for many hours can be obtained by combining various pharmaceutical preparations which differ from each other in the amount of the coating layer or In a kind of a component of the coating layer, according to the present Invention.

The pharmaceutical preparation of the present Invention wherein the coating layer of a slightly water-permeable acrylic polymer is futher coated with ethylcellulose, hydroxypropylcellulose or the like, has a following adventage. That Is, beceuse the dissolution rate of a medicinel compound efter e leg time In such pharmaceutical preparation is smaller than that in a pharmaceuticel preparation whose coating layer of an acrylic polymer and a water-repellent salt is not further coated, the most suitable dissolution pattern cen be obtained by employing the above-mentioned coating layer In accordance with a kind of medicinal active Ingredient. In addition, these pharmaceutical preparations also have an advantage of being useful for preventing the aggregation of the preparetions, which occurs during preparing them.

Further the pharmaceutical preparation wherein the layer of a medicinal compound is provided around the coating layer of an acrylic polymer can stert the dissolution of the inside medicinal compound when the blood concentretion origineted In the outside medicinel compound has lowered after its dissolution followed by the rise of its concentration, by edjusting the amounts of the medicinal compound layer and en ecrylic polymer layer or providing another coating layer of hydroxypropylcellulose or the like around the layer of a medicinal compound. Therefore, the pharmaceutical preparetion of the present Invention hes en edventege thet it can be administered as a pharmaceutical preparation suitable for administretion a day.

The present Invention Is more specifically described and explained by meens of the following Test Examples end Examples in which all percents and parts are by weight unless otherwise noted. It is to be understood that the present invention is not limited to the Examples, and various changes and modifications mey be made in the Invention without departing from the spirit and scope thereof.

Test Example 1

(1) Preparation

Nonpareil (granulated sucrose, from Freund Industrial Co. Ltd., Japan) having the diameter of 350 to 500 μm (80 g) was put into the centrifugal fluidizing type granulating and coating apparatus (CF-360EX Type, made by Freund Industrial Co. Ltd., Japan) and rolled in it.

Thereto was gradually added fine powder of diltiazem hydrochloride (900 g) with spraying a solution of polyvinylpyrrolidone (20 g) dissolved in a mixture of water and ethanol (3:2) (640 g). Nonpareil was thus coated around its surface with diltiazem hydrochloride to obtain plain granule containing diltiazem hydrochloride in the amount of 90 %.

Then this plain granule was spray-coated with a solution containing 30 parts of Eudragit RS, 10 parts of calcium stearate and 3 parts of triethyl citrate to obtain various controlled release pharmaceutical preparations (a) to (e) containing diltiazem hydrochloride, which differ from each other in the amount of the coating layer on the plain granule as shown in Table 1.

Table 1

Controlled release pharmaceutical preparation	Amount of coating layer*
(a)	12
(b)	14
(c)	16
(d)	20
(e)	22

* Amount of coating layer (g) per 100 g of plain granule

(2) Comparison of dissolution patterns

① The dissolution test according to the puddle method (37°C, water, 100 rpm) based on the specification of the dissolution test under 11th revised japanese Pharmacopoeia (JPXI) was carried out with respect to each pharmaceutical preparation obtained in the above.

Plain granule containing diltiazem hydrochloride which was not yet coated was used as a control preparation.

② The dissolution test according to the same condition as in① was carried out with respect to the pharmaceutical preparation (d) in Table 1, with first fluid (JPXI), second fluid (JPXI) and water.

(3) Result

The result of the dissolution test in① is shown in Fig. 1. It is recognized that according to the pharmaceutical preparation of the present invention, the medicinal compounds are completely released and their dissolution patterns show sigmoid type in water, although the lag time until the start of the dissolution is prolonged according as the increase of the amount of the coating layer in the pharmaceutical preparation.

The result of the dissolution test in② is shown in Fig. 2. It is shown that the pharmaceutical preparation of the present invention shows th same dissolution patterns both with first fluid and second fluid as that with water. This result shows that the pharmaceutical preparation of the present invention has the pH-independent dissolution property. Therefore, it is recognized that according to the pharmaceutical preparation of the present

invention, a medicinal compound dissolves immediately aft r a lag time irrespectiv of the pH change in the digestive tract.

Test exampl 2

The controlled release pharmaceutical preparation (d) obtained in Test Example 1 was orally administered (dose: 100 mg as the amount of dlltlazem hydrochloride) to dogs. After administration the blood was collected from vein at fixed times. The plasma concentration of diltiazem hydrochloride was measured by high performance liquid chromatography.

The result is shown in Fig. 3. It is recognized that the plasma concentration level is still high 30 hours later after the lag time of 8 hours.

Test Example 3

The controlled release pharmaceutical preparations (a) (373 g) and (d) (800 g) obtained in the Test Example 1 and the plain granule (111 g) containing diltiazem hydrochloride were mixed. The mixture (128 mg) containing 100 mg of diltiazem hydrochloride was filled into a gelatin capsule to obtain a controlled release capsule.

Then the dissolution test according to the puddle method (37°C, water, 100 rpm) under JPXI was carried out in the same manner as in Test Example 1 with respect to the controlled release capsule obtained in the above.

The result of the dissolution test shows the durative dissolution pattern for 24 hours as shown in Fig. 4. Therefore, it is clear that a preparation can be designed to release a drug continuously for long hours by combining various pharmaceutical preparations of the present invention.

Example 1

Nonpareil 103 (granulated sucrose, from Freund Industrial Co. Ltd., Japan) which was a spherically granulated sucrose having the diameter of 350 to 500 μm (800 g) was put into the centrifugal fluidizing type granulating and coating apparatus (made by Freund Industrial Co. Ltd., Japan hereinafter referred to as CF apparatus) and rolled in it. Thereto was gradually spread fine powder of diltiazem hydrochloride (9 kg) with spraying a solution of polyvinylpyrrolidone (200 g) in a mixture of ethanol and water (2 : 3) (6. 4 kg). Plain granule having the diameter of 12 to 20 mesh (1400 to 840 μm) containing diltiazem hydrochloride, wherein Nonpareil was coated around its surface with diltiazem hydrochloride, was thus prepared. Then the obtained plain granule (1 kg) containing diltiazem hydrochloride was put into CF apparatus and spray-coated with a solution consisting of Eudragit RS (a copolymer of ethyl acrylate, methyl methacrylate and β-acryloyloxyethyltrimethylammonium chloride, from Röhm Pharma, Germany) (84 g), calcium stearate (28 g), triethyl citrate (8 g), ethanol (160 g) and water (320 g). After coating, the granule was dried by heating at 60°C for 16 hours to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride (yield: 1. 12 kg).

Example 2

The procedure was carried out in the same manner as in Example 1 except that a mixture of Eudragit RS (112 g), calcium stearate (37 g), triethyl citrate (11 g), ethanol (210 g) and water (430 g) was used as a coating solution to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride (yield: 1.16 kg).

Example 3

The procedure was carried out in the same manner as in Example 1 except that a mixture of Eudragit RS (140 g), calcium stearate (47 g), triethyl citrate (14 g), ethanol (267 g) and water (533 g) was used as a coating solution to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride (yield: 1.2 kg).

Example 4

The procedure was carried out in the same manner as in Exampl 3 except that magnesium stearate (47 g) was used instead of calcium stearate to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride (yield: 1.2 kg).

Example 5

Th procedur was carried out in the same manner as in Example 3 exc pt that tributyl acetylcitrate (14 g) was used instead of triethyl citrate as a plasticizer to obtain a controlled r lease pharmaceutical preparation containing diltiazem hydrochloride (yield: 1.2 kg).

Example 6

Combo

The procedure was carried out in the same manner as in Example 3 except that both Eudragit RS (126 g) and Eudragit RL (14 g) were used instead of Eudragit RS (140 g) to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride (yield: 1.2 kg).

Example 7

The controlled release pharmaceutical preparation (0.56 kg) containing diltiazem hydrochloride obtained in the same manner as in Example 3 was put into CF apparatus and spray-coated with a coating solution consisting of ethylcellulose (9.5 g), hydroxypropylcellulose (0.5 g), ethanol (59 g) and water (32 g). Then the preparation was dried at 60°C for 16 hours to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride (yield: 0.57 kg).

Example 8

The controlled release pharmaceutical preparation (1.12 kg) containing diltiazem hydrochloride obtained in the same manner as in Example 3 was put into CF apparatus and spray-coated with a coating solution consisting of diltiazem hydrochloride (151 g), polyvinylpyrrolidone (12 g), ethanol (87 g) and water (203 g). Then the preparation was dried at 60°C for 18 hows to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride, wherein the part which rapidly released diltiazem hydrochloride was provided in its surface layer.

Example 9

To diltiazem chloride (4.8 kg) was added a solution of polyvinylpyrrolidone (K30) (0.15 kg) dissolved in water (0.3 kg). The mixture was kneaded, dried at 45°C for 4 hows and grannulated by sieving with 32 mesh sieve. To the obtained granule (4.5 kg) was added magnesium stearate (45 g) and the mixed powder thereof was tabletted to give plain tablets containing diltiazem hydrochloride, which have the diameter of 5 mm and the weight of 50 mg per tablet.

Then plain tablets (4.0 kg) were put into the coating apparatus (Hi-coater, made by Freund Industrial Co. Ltd., Japan) and spray-coated with a solution consisting of Eudragit RS (224 g), calcium stearate (74 g), triethyl citrate (22 g), ethanol (420 g) and water (860 g). Then the tablets were dried by heating at 60°C for 16 hours to obtain controlled release tablets containing diltiazem hydrochloride (yield: 4.3 kg).

Example 10

Nonpareil 103 which was a spherically granulated sucrose having the diameter of 350 to 500 μm (1500 g) was put into CF apparatus and rolled in it. Thereto was gradually spread fine powder of nicotinamide (NA) (900 g) with spraying a solution of sucrose (135 g) in a mixture (465 g) of ethanol and water (1:3). The plain granule having the diameter of 12 to 20 mesh (1400 to 840 μm) containing NA, wherein Nonpareil was coated around its surface with NA, was thus prepared.

Then the obtained plain granule (0.5 kg) containing NA was put into CF apparatus and spray-coated with a solution consisiting of Eudragit RS (105 g), calcium stearate (35 g), triethyl citrate (11 g), ethanol (200 g) and water (400 g). Then the granule was dried by heating at 60°C for 16 hours to obtain a controlled release pharmaceutical preparation containing NA (yield: 0.56 kg).

Example 11

The procedure was carried out in the same manner as in Example 10 except that phenylpropanolamine hydrochloride was used instead of NA to obtain a controlled release pharmaceutical preparation containing phenylpropanolamin hydrochloride (yield: 0.56 kg).

Example 12

The proc dure was carried out in the same menner as in Example 10 except that bisoprolol fumarate was used instead of NA to obtain a controlled release pharmaceutical preparation containing bisoprolol fumarate (yield: 0.56 kg).

Exemple 13

The procedure was carried out in the same manner as in Example 10 except that ascorbic acid was used insteed of NA to obtaln e controlled release phermeceutlcal preperation conteining escorblc ecld (yleld: 0.56 kg).

Exemple 14

The procedure wes cerried out in the same menner as in Exemple 10 except that thlemine hydrochloride was used instead of NA to obtain a controlled release pharmaceutical preparation containing thiamine hydrochloride (yield: 0.56 kg).

Example 15

The procedure was carried out in the seme manner as in Example 10 except that pyridoxine hydrochloride was used instead of NA to obtain a controlled release pharmaceutical preparation containing pyridoxine hydrochloride (yleld: 0.56 kg).

Example 16

Nonpareil 103 which was a spherically granulated sucrose having the diameter of 500 to 710 μm (1.04 kg) was put into CF epperatus end rolled In It. Thereto wes greduelly spreed a mixed powder of fine powder of (+)-(2S, 3S)-3-acetoxy-8-chloro-5-[2-(dimethylamino)ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)- 1,5-benzothiazepin-4(5H)-one · maleate (hereinafter referred to as Clentiazem) (1.176 kg) and succinic ecid (1.96 kg) with spraying a solution of sucrose (0.78 kg) in the mixture of ethanol and weter (1 : 3) (2.22 kg). The plain grenule having the diameter of 12 to 24 mesh (1400 to 710 μm) containing Clentiazem, wherein Nonpareil was coated around its surfece with Clentiazem, wes thus prepared.

Then the obtained plein granule (1 kg) containing Clentiazem was put into CF apparatus and spray-coated with a solution consisiting of Eudragit RS (279 g), calcium stearate (93 g), triethyl citrate (28 g), ethanol (533 g) end weter (1067 g). After coeting, the grenule wes drled by heating et 60°C for 16 hours to obtein e controlled release pharmaceutical preparation containing Clentiazem (yield: 1.38 kg).

In eddltion to the Ingredients used In the Exemples, other Ingredients can be used In the Examples es set forth In the specification to obtaln substentielly the seme results.

Claims

1. A controlled release phermeceutical preparation comprising e core containing e medicinel compound and a coating layer containing a water-repellent salt and a water-insoluble end slightly water-permeeble acrylic polymer hevlng trimethylemmonlumethyl groups.

2. A pharmaceutlcal preparation of Claim 1, wherein 0.5 to 5 parts weight of the acrylic polymer is contained per part by welght of the water-repellent selt In the coatlng leyer.

3. A phermaceutical preperatlon of Clelm 1 or Clelm 2, wherein the ecrylic polymer Is a weter-Insoluble end slightly water-permeable copolymer of ethyl ecrylate, methyl methacryiete end $_b$-acryloyloxyethyltrimethylammonium chloride and the water-repellent salt is an alkeline earth metal stearate.

4. A pharmac utical preparation of any one of claims 1 to 3, wherein another coating layer mad of at least one materlal selected from th group consisting of ethylcellullose, hydroxypypropylcellulose end e medicinal compound is provided around the coating layer containing a water-repellent selt and a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl groups.

5. A pharmaceutical preparation of any one of Claims 1 to 4 wher in the medicinal compound in the core is a calcium antagonist, an antiasthmatic agent, an antipyretic, an analgesic or an antihyperglycemic agent.

6. A pharmaceutical preparation as claimed in claim 5 wh rein the medicinal compound in the core is diltiazem hydrochloride, verapamil hydrochloride, nicardipine, nitrendipine, nimodipine, theophylline or trimetaquinol.

7. A pharmaceutical preparation of any one of claims 1 to 6 wherein the core also comprises one or more excipients, binders, lubricants, aggregation preventing agents or solubilizers.

Claims for the following Contracting States: ES and GR

1. A method of preparing a controlled release pharmaceutical preparation comprising a core containing a medicinal compound and a coating layer containing a water-repellent salt and a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl groups comprising the steps of forming the core containing said medicinal compound and coating said core with the coating layer.

2. A method as claimed in Claim 1 wherein 0.5 to 5 parts weight of the acrylic polymer is contained per part by weight of the water-repellent salt in the coating layer.

3. A method as claimed in Claim 1 or Claim 2 wherein the acrylic polymer is a water-insoluble and slightly water-permeable copolymer of ethyl acrylate, methyl methacrylate and $_b$-acryloyloxyetheytrimethylammonium chloride and the water-repellent salt is an alkaline earth metal stearate.

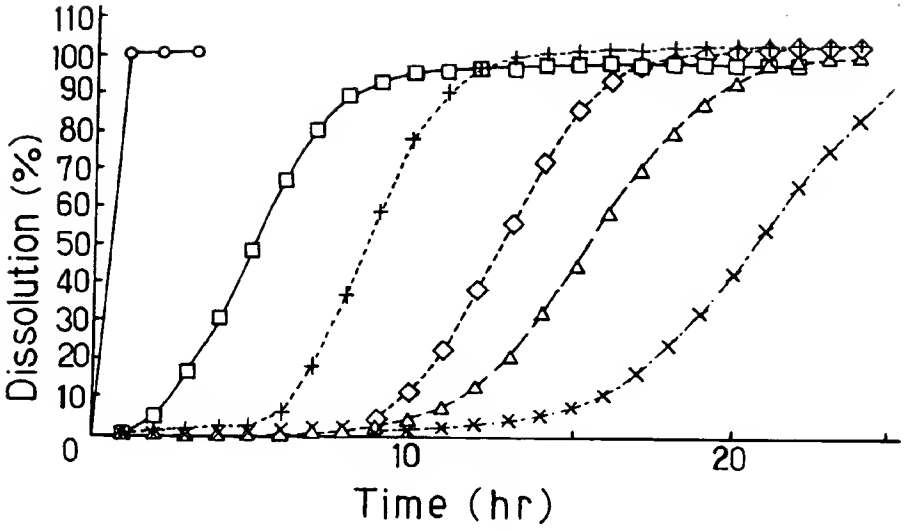
4. A method as claimed in any one of Claim 1 to 3 wherein another coating layer made of at least one material selected from the group consisting of ethylcellullose, hydroxypropylcellulose and a medicinal compound is provided around the coating layer containing a water-repellent salt and a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl groups.

5. A method as claimed in any one of Claims 1 to 4 wherein the medicinal compound in the core is a calcium antagonist, an antiasthmatic agent, an antipyretic, an analgesic or an antihyperglycemic agent.

6. A method as claimed in Claim 5 wherein the medicinal compound in the core is diltiazem hydrochloride, verapamil hydrochloride, nicardipine, nitrendipine, nimodipine, theophylline or trimetaquinol.

7. A method as claimed in any one of Claims 1 to 6 wherein the core also comprises one or more excipients, binders, lubricants, aggregation preventing agents or solubilizers.

FIG. 1



o—o Plain granule containing diltiazem hydrochloride (control)

□—□ Controlled release pharmaceutical preparation (a)

+----+ Controlled release pharmaceutical preparation (b)

◇---◇ Controlled release pharmaceutical preparation (c)

△--△ Controlled release pharmaceutical preparation (d)

×-·-× Controlled release pharmaceutical preparation (e)

FIG. 2

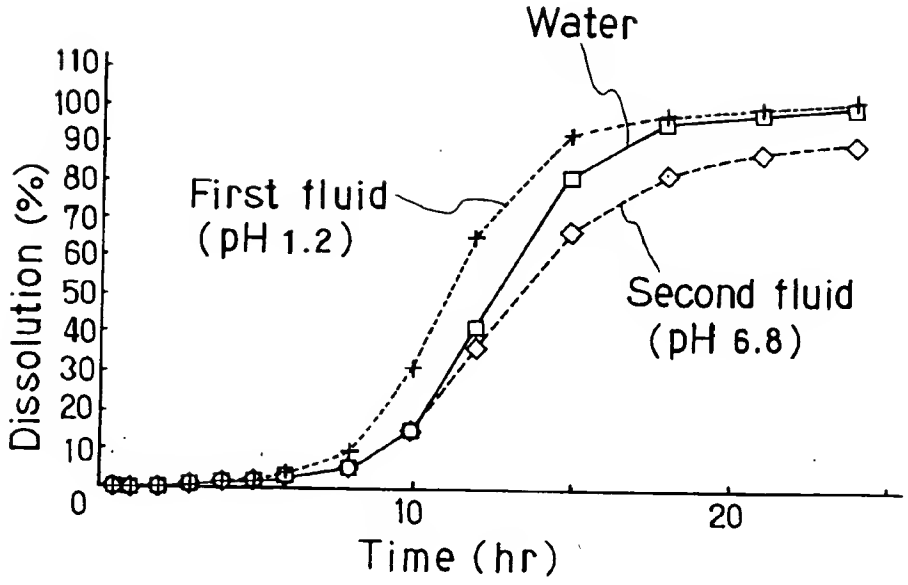

Water
First fluid
(pH 1.2)
Second fluid
(pH 6.8)
Dissolution (%)
110
100
90
80
70
60
50
40
30
20
10
0
10
20
Time (hr)

FIG.3

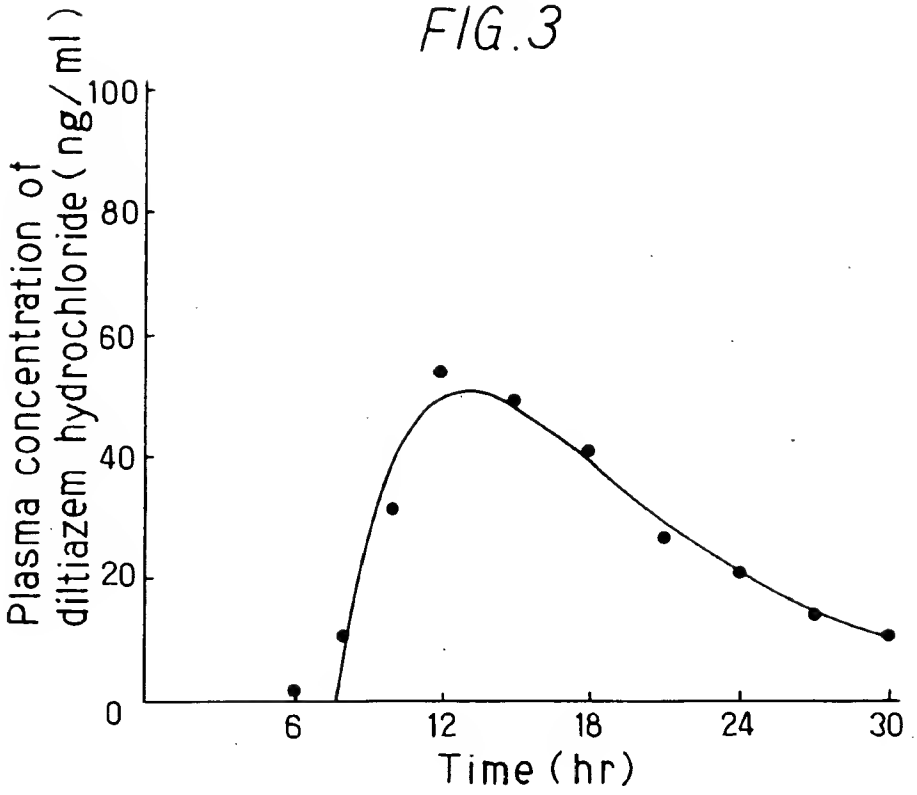
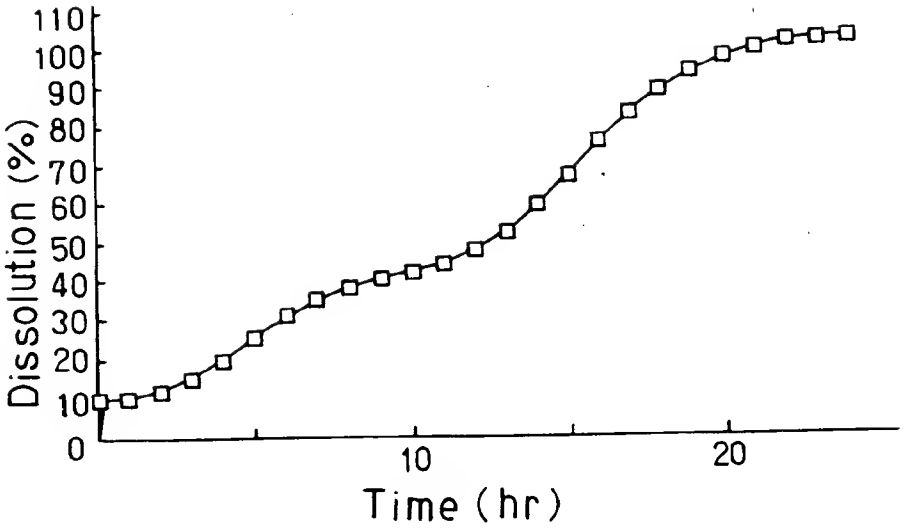

Plasma concentration of diltiazem hydrochloride (ng/ml)
100
80
60
40
20
0
6
12
18
24
30
Time (hr)

FIG.4



European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 30 5834

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,X	EP-A-0 386 440 (BAYER AG) * Claim 1; page 4, line 37 - page 6, line 2; page 6, lines 23-27; examples 2-6 *	1-3,5-7	A 61 K 9/54 A 61 K 9/52
Y	---	4	
Y	EP-A-0 315 414 (TANABE SEIYAKU CO., LTD) * Claims 1,7,10,12,13; page 2, lines 17-20,31-34; page 3, lines 1-5,39-44 * -----	4	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13-09-1991	VENTURA AMAT A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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